REMARKS

Claims 1, 2, 4-8 and 12-15 are currently pending. A copy of all the pending claims is provided in an appendix for the Examiner's convenience.

Claims 1, 4 and 15 have been amended for clarity. Support is found, for example, at page 11, lines 7-11.

Claim 8 is amended to state the method of preparation of the population and to specify the possible cell types of the population. Support is found, for example, at page 11, lines 3-11.

Claim 13 is amended to depend from Claim 16 as well as Claim 12. Suuport is found, for example, in original Claim 12.

New Claim 16 is added. Support is found, for example, in original Claim 12.

Rejection Under 35 U.S.C. § 112

Claims 1, 2, 4-7 and 15 are rejected under 35 U.S.C. § 112, second paragraph for reciting a phrase that lacks antecedent basis.

Claims 1, 4 and 15 have been amended to recite that each named cell comprises RET protein. Therefore, these claims provide proper antecedent basis and Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

Claim 8 is rejected under 35 U.S.C. § 102(b) as being anticipated by Stemple et al., *Cell* 71:973-985 (1992) (Stemple I). Applicants respectfully traverse.

To anticipate a claim under 35 U.S.C. § 102, each element of the claim must be taught or suggested in a single prior art reference. Claim 8, as amended, is directed to a substantially pure population of neural crest derived neural progenitor cells prepared by antibody binding, where the cells are NNP cells.

Stemple I discloses isolating cells with an antibody and producing clones and subclones of these cells. The population of cells isolated by antibody binding is clearly

not a substantially pure population of NNP cells. The vast majority of the cells disclosed in Stemple I were capable of giving rise to both neuronal and nonneuronal cells (*see* page 976, left column, last sentence before first full paragraph). These were the only populations of cells prepared by antibody binding.

For the reasons discussed above, Claim 8 is not anticipated by Stemple I. Therefore, Applicants respectfully request that this 35 U.S.C. § 102(b) rejection be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4-8 and 12-15 are rejected under 35 U.S.C. § 103(a) as bing obvious over Lo et al., *Perspectives Dev. Neurobiol.* 2:191-201 (1994) (Lo), Stemple *et al.*, *Dev. Biol.* 159:12-23 (1993) (Stemple II), Stemple *et al.*, *Cell* 71:973-985 (1992.) (Stemple I), and Martucciello *et al.*, *J. Ped. Surg.* 30(3):433-436 (1995) (Martucciello). Applicants respectfully traverse.

For a rejection under 35 U.S.C. § 103 to be proper, it must be shown that: 1) each element of a claim is disclosed or suggested in the prior art; 2) the prior art provided motivation to combine and/or modify prior art disclosures to obtain the claimed invention; and 3) the skilled artisan would have a reasonable expectation of successfully obtaining the claimed invention. Applicants submit that all of these have not been met in the present rejection.

Applicants first note that in the initial Office Action, no specific motivation is provided or suggested in the prior art that would inspire the skilled artisan to combine the cited teaching to obtain the present invention. In subsequent Office Actions, it is recited that, "The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art." (citing *In re McLaughlin*, 170 USPQ 20 (CCPA 1971)). Perhaps Applicants misunderstand the assertion, but these Office Actions appear to suggest that the combination is first made, then looked at to see if it would be suggested to the skilled artisan. This approach appears to condone what would otherwise be considered impermissible hindsight reconstruction. The Office Actions appear to suggest that the combination should suggest itself once it is made, rather than the

references being required to suggest the combination. Applicants submit that, assuming this interpretation is correct, this is not a proper approach to determining motivation to combine references. While references need not literally suggest combination, the suggestion must be found in the individual art, not *post hoc*.

All Elements Not Taught

Claims 1 and 2 are directed to a composition comprising neural crest progenitor cells and an antibody specifically bound to the RET sequence. Claims 4-7 are directed to a method for enrichment of neural progenitor cells comprising combining neural crest derived cells comprising neural progenitor cells with an antibody and isolating RET positive cells. Claims 8-14 are directed to a substantially pure population of neural crest derived NNP cells prepared using an antibody. Claim 15 is directed to a method for the enrichment of neural progenitor cells comprising combining cells comprising neural progenitor cells comprising RET protein with a monoclonal antibody that specifically binds to RET protein and selecting RET positive cells. In each of the claims except Claim 8, the element of an antibody specifically bound to a RET protein or the binding thereof on a neural crest derived neural progenitor cell is found. This element is not taught or suggested in any of the cited references. Furthermore, a population such as is described in Claim 8 is neither taught nor suggested. In fact, Lo teaches away from the population of Claim 12 by teaching in figure 6 that glial progenitor cells are RET-. The present disclosure teaches that some NNP's, which may be glial progenitors, are RET+.

No Motivation to Combine or Modify Prior Art

As discussed above, the motivation to combine and/or modify prior art must come from the individual references themselves, not *ad hoc* once a combination is produced that appears to fill the criteria for obviousness. Nevertheless, the motivation to combine and/or modify the cited art to obtain the present invention is not found therein.

The first Office Action for this case states that it would be obvious to use antibodies such as disclosed in Martucciello for imunological fractionation of RET+ cells by conventional methods such as disclosed in Stemple I because Stemple II says such methods

have been useful and Lo teaches that RET is a useful marker for early neural crest cell lineage (page 12 of Office Action mailed 4/1/98). A consideration of this conclusion and the prior art shows that it is not only beyond the scope of what is suggested in the art, but it is not sufficient to obtain the present invention.

First of all, Lo only teaches in situ hybridization of RET mRNA. Therefore, while expression of the gene is shown, expression of the protein is not. Nor is the form of the protein, if expressed, shown. Martucciello teaches that the RET protein had only been characterized in cancer cells and, therefore, had not been characterized in neural crest derived neural progenitor cells. Furthermore, the antibodies of Martuciello are directed to RET protein expressed in E. coli. It is well known that eukaryotic post-translational processing is frequently not replicated in prokaryotic systems. Furthermore, differential processing of proteins in developing, mature and cancerous cells is also well known. Therefore, antibodies that bind to adult RET may not bind to RET expressed in developing cells, particularly monoclonal antibodies, because of their singular antigen recognition. Stemple I teaches that the choice of antigen to use for isolating cells should be carefully made. The use of the LNGFR in Stemple I was based on the solid knowledge, multiply confirmed, that the receptor protein was expressed in neural crest cells and several antibodies were available that were known to bind to the extracellular epitopes of the receptor (page 974, first full paragraph). Such information is not shown in the prior art for RET in neural crest derived neural progenitor cells. Stemple II provides no disclosure of RET protein expression nor antibodies to it in neural crest cells.

While immunologic fractionation of neural crest cells is clearly suggest in the prior art, the use of antibodies against RET for such a task is not. The confidence of protein expression and antigenic potential that Stemple I makes clear is required cannot be found. At best, there is a suggestion to try, but this is not the standard for obviousness under the statute.

No Reasonable Expectation of Success

As discussed above, the lack of information regarding RET in neural crest derived neural progenitor cells left inherent uncertainties at the time of invention as to whether these

cells expressed the RET protein or whether , even if they did, that it would be sufficiently antigenic to allow antibodies to specifically bind so as to permit enrichment of such cells. With this inherent uncertainty, the ordinary skilled artisan would not have a reasonable expectation that such methods for enrichment, or compositions or populations of cells as found in the present claims, would result, even if the steps of the methods were tried.

For the reasons discussed above, Claims 1, 2, 4-8, and 12-15 are not obvious over Lo, Stemp II, Stemp I and Martuciello. Therefore, Applicants respectfully request that this 35 U.S.C. § 103(a) rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If the Examiner believes a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned attorney.

Respectfully submitted,

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APPENDIX:

1. (Thrice amended) A composition comprising a monoclonal antibody and a cell selected from the group consisting of a multipotent neuronal progenitor (proNP) cell, a nonneuronal progenitor (NNP) cell and a committed neuronal progenitor (NP) cell, each of which comprise RET protein, wherein said monoclonal antibody is specifically bound to all of part of the RET sequence on said cell.

2. (Twice Amended) The composition according to claim 1, wherein said sequence consists essentially of the extracellular domain of RET.

4. (Thrice Amended) A method for the enrichment of neural progenitor cells comprising RET protein, said method comprising:

a) combining a mixed population of cells comprising neural-crest derived cells comprising neural progenitor cells with an antibody that specifically binds to all of part of the RET sequence; and

b) selecting for RET positive cells.

5. (Amended) The method according to claim 4 wherein said antibody is selected from the group consisting of polyclonal antibody, monoclonal antibody, antibody fragments, and single chain antibody.

6. (Amended) The method according to claim 5, wherein said antibody is fluorochrome conjugated.

7. (Twice Amended) A method according to claim 6, wherein said selecting with said fluorochrome conjugated antibody is by flow cytometry.

8. (Thrice Amended) A substantially pure population of neural crest derived neural progenitor cells prepared using antibody binding, where said cells are nonneuronal progenitor (NNP) cells.

12. (Amended) The population according to claim 8 wherein said neural progenitor cells are bound to an antibody that specifically binds to RET antigen.

13. (Twice Amended) The population according to claim 12 or 16 wherein said antibody is selected from the group consisting of polyclonal antibody, monoclonal antibody, antibody fragments, and single chain antibody.

14. (Amended) The population according to claim 13 wherein said antibody is a monoclonal antibody.

15. (Twice Amended) A method for the enrichment of neural progenitor cells, said method comprising:

a) combining a mixed population of cells comprising neural-crest derived cells comprising neural progenitor cells comprising RET protein with a monoclonal antibody that specifically binds to all of part of the RET sequence; and

b) selecting for RET positive cells.